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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,591	08/27/2003	Noubar B. Afeyan	COTH-P02-001	7918

28120 7590 12/12/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER

MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/650,591	Applicant(s) AFEYAN ET AL.	
	Examiner Mohammad Meah	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1, 4-13 14-17, 18 19-21, 22-27, 30-38, 41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1, 4-13 14-17, 18 19-21, 22-27, 30-38, 41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/2/06</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

claims 1 and 3-41 were examined in the previous action. With supplemental amendment of this application, the applicant, on dates 9/29/06, cancelled claim 2, amended claims 1, 14-17, 19-21, 31-32, 35-36, 41 and withdrew 3, 28 and 29.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

Rejection of claims 8-16, 31-31 and 36 under USC 112 2nd *paragraph* requirement is withdrawn after amendment of the claims by the applicant.

Claims 6-7, 16 remain rejected under USC 112 2nd *paragraph* requirement
Because the recitation of the term “potency” makes these claims confusing.

Applicants arguments at page 7 of their amendments against rejection of claims 6-7, 16 under 35 U.S.C 112, 2nd paragraph requirement are acknowledged but not found persuasive because: Applicant appears to argue that potency is term used in biochemistry for “enzyme activity”. If that is so then applicant should replace “potency ” by “enzyme activity” a commonly known term in art.

35 U.S.C 112

Written Description requirement

Rejection of claims 1-2, 4-25, 28--41 under USC 112 1st paragraph Written Description requirement is withdrawn after amendment of the claims by the applicant.

Enablement requirement

Rejection of claims 1, 4-5, 13-27, 30, 37 under USC 112 1st paragraph enablement requirement is withdrawn after amendment of the claims by the applicant.

However Claims 6-13, 31, 35-36, 38-40 remain rejected under USC 112 1st paragraph enablement requirement.

Claims 6-13 and 31 recite many kinetic properties (with specific kinetic parameters) of fusion proteins. As explained in the previous office action, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of adzymes or fusion proteins attached to these kinetic parameters. Since specific kinetic parameters depend on type of individual protease, individual targeting domain (antibody or protein) it is linked to as well as on the type of conjugation with individual linker peptide and individual substrate polypeptide the adzyme acts on, achievement of desired kinetic values for the broad class of adzymes (made via conjugation of any protease conjugated through board

Art Unit: 1652

class of linker polypeptides with broad class of targeting domains) acting on board class of substrates is highly unlikely. Specification disclose kinetic parameters for few such adzymes.

Claims 35-36 and 38-40 remain rejected under USC 112 1st paragraph enablement requirement.

Claims 35-36 recite an adzyme that catalyze the proteolytic cleavage of any substrate polypeptide producing any product which inhibits the substrate or the proteolytic cleavage of adzyme. The claims broadly recite the use of **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. The specification fails to describe how any cleavage-product of any substrate polypeptide inhibits the substrate or the proteolytic cleavage of adzyme. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of substrates and their by-products as discussed above. As the structure of the claimed substrates and their by-products are not defined in any way, one of ordinary skill in the art would not be able to make and use any of such substrates without undue experimentation to first find what substrate and their by-product in fact fall within the claimed class. Furthermore, the claimed class of substrates and their by-products is likely to include many compounds, which one of ordinary skill in the art would be unable to make and use without undue experimentation, even if it was known or expected that the substance be within the scope of the claims.

Claims 38-40 recite an adzyme composition wherein autocatalytic proteolysis is inhibited by any means or especially by inclusion of a reversible inhibitor but it is not clear that there are available reversible inhibitors for any protease nor are other means of formulating an adzyme composition to prevent auto proteolysis is taught..

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any substrate and their by-product. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

CLAIM Rejection - 35 U.S.C 102

The 102 rejections of claims 1, 4-27 (dependent on claim 1) and 30, 34, 37-38, 41 dependent on claim 1) under 35 U.S.C. 102 using Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), of the previous office action are still remained applicable.

Claims 1, 4, 14, 16-25, 28, 30-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485) as explained by the previous office action.

Claims 1, 4, 18-21, 30-34 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) as explained by the previous office action.

Claims 1, 4, 14, 16-25, 28, 30-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792) as explained by the previous office action.

Claims 6-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) and Chen et al. (US 2003/0068792) as explained by the previous office action.

Applicant's argument, that Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), does not teach fusion proteins that are resistant to autoproteolytic cleavage is not found to be persuasive because although the cited references did not mention the resistivity to auto proteolysis, there is no available evidence to suggest that they are labile to autoproteolysis and furthermore as their fusion proteins are stable enough to show protease activity to cleave substrate polypeptide they must inherently be resistant to self cleavage. Amended claims 1, 4-27 (dependent on claim 1) and 30, 34, 37-38, 41 are therefore rejected under 35 U.S.C. 102 using Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792

Furthermore, in view of the amendment of the claims 1, 4, 14-17, 21, 31-3235, 41-43 by applicant's and lack of explicit teaching of resistance to autoproteolysis a new ground(s) of rejection as presented below is applied to address what appears to be applicants preferred embodiments.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4 14-17, 18 19-21, 22-27, 30 -38, 41 are rejected under 35 U.S.C. 103(a) by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), Guo et al. (Biotec and Biong 2000, 70, 456-463) in view of Sallberg et al. (US 6960569) or whitcomb et al. (US PAT 6406846).

Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator (Urokinase – a serine protease) is fused with fibrin-specific antibody (variable region Fv) molecule. The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. This fusion protein target cells (in this case blood clot) than cleave plasminogen to release active plasmin (an enzyme) resulting plasmin in turn inhibit/digest extracellular signalling molecules, act on cytokine transforming growth factor or lyse clot. Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator where fibrin-specific antibody (variable region Fv) molecule is fused with single chain Urokinase (a serine protease). The resulting

Art Unit: 1652

fusion protein shows 2.5-fold increase of the fibrinolytic potency. **Although Holvoet et al. does not disclose all the specific kinetic properties of the instant claims, the fusion protein had a 2.5-13 fold increase of the fibrinolytic potency compared to unconjugated enzyme. Fusion protein of single chain Urokinase fusion to antibody had the following kinetic parameters: $K_a = 5.5 \times 10^9 \text{ M}^{-1}$ $K_m = 12 \text{ microM}$ and $K_{cat} = 0.12 \times 10^{-6} \text{ M}^{-1} / \text{sec}^{-1}$ for the fusion protein compare to $0.02 \times 10^{-6} \text{ M}^{-1} / \text{sec}^{-1}$ for unconjugated enzyme.**

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyse degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) **to the target with or without a linker and resulting fusion protein** has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc.

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to immunoglobulin or fragment or antibody to the target proteins such as kinases, lipases, and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the **target and**

Art Unit: 1652

then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Chen et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme

Guo et al. teach fusion proteins wherein enzyme (ASNase) conjugated to immunoglobulin or fragment or antibody (scFV) by a linker polypeptide (Gly₄Ser)₃.

Whitcomb et al. (US PAT4510251) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is fairly stable to proteolytic cleavage and also teach that mesotrypsin rapidly degrades and inactivate zymogens and other polypeptides.

Sallberg et al. (US 6960569) teach fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolytic cleavage)

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo et al. to targeting domain as thought by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792) and use the resulting

Art Unit: 1652

adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-25, 30-41 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-25, 30-41 of copending Application No.10792498. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain and claim 1 of copending application 10792498 comprises an adzyme comprising mesotrypsin a protease as catalytic domain. The remainder of these two claims is identical as are the dependent claims thereof. As such the claims of the instant application and those of the copending application differ only in the scope of protease within the claimed adzymes. Serine protease is sub species of protease. Therefore, claims 1-2, 4-25, 28, 30-41 herein are anticipated by claims 1-2, 4-25, 28, 30-41 of copending 10792498.

Claims 1, 4-25, 28-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10,650592. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Art Unit: 1652

Claim 1 of instant application comprises an adzyme comprising protease as catalytic domain fused with a targeting domain, acts on an extra cellular substrate polypeptide resulting the inhibition of receptor-mediated signaling activity of the substrate and claims 1, 4-6 of copending application 10,650,592 comprises an adzyme comprising any enzyme as catalytic domain, fused with a targeting moiety, acts on any substrate (claims 1, 4), any polypeptide or extra cellular substrate polypeptide (5-6) and inhibit the substrate activity. Claim 1, 4-6 of the copending application further differ in scope from the instant claims in that claim 1 of the copending application recites specific kinetic parameters of the adzyme, claim 4 of the copending application recites that the product produced by the action of the enzyme on the substrate is an antagonist of the substrate and claim 5 of the copending application recites that adzyme is resistant to cleavage by the catalytic domain. These additional limitations are recited in the instant application only in dependent claims. However, the specification of copending application 10/650,592 discloses the following specific embodiments of adzymes within the scope of claims 1, 4-6, 7-38, 40-46, 52-60, 66-104 and 107-134 therein which support the genera of adzymes recited in the claim of the copending application: prothombin/scFv α Ha, trypsin/sp55. It would have been obvious to one of ordinary skill in the art to select these specific embodiments of genera of the copending application to practice the invention thereof. These adzymes anticipate the instant claims herein.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

Art Unit: 1652

more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

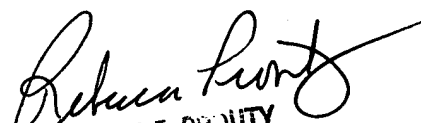
Mohammad Younus Meah, PhD

Examiner, Art Unit 1652

Recombinant Enzymes, 3C31 Remsen Bld

400 Dulany Street, Alexandria, VA 22314

Telephone: 517-272-1261


REBECCA E. PROITY
PRIMARY EXAMINER
GROUP 1600
1600